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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,697	08/09/2001	Yoshihide Iwaki	GY-YY-5095 / 500569.20073	6474

26418 7590 11/13/2003

REED SMITH, LLP
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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,697	IWAKI ET AL.	
	Examin r	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/16/03*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-9 and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-9 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed September 16, 2003. Currently, claims 1, 5-9, 13-16 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn.

4. This action contains new grounds of rejection necessitated by amendment.

Priority

5. This application claims priority to Japan 2000-241773 and Japan 2001-161199, filed 8/9/00 and 5/29/01, respectively.

Certified copies were received September 12, 2003.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Sequence Rules

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

It is noted that the specification contains sequences which are not identified by SEQ ID NO:. For example, page 18 and 23, contain probe molecules which are not identified by SEQ ID NO:. Appropriate correction is required.

The instant specification does not appear to have been amended.

New Matter

7. Claims 1, 5-9, 13-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "remove all of the thickening agent" is included, in Claim 1 and 9. The amendment does not appear to point to the specification for support for the amendment. However, the specification does not describe or discuss "remove all of the thickening agent". Instead the specification describes "so as to almost completely remove the thickening agent from the glass plate" (page 24, lines 25-26). This description does not support "remove all of the thickening agent". The concept of ""remove all of the thickening agent" does not appear to be part of the originally filed invention. Therefore, ""remove all of the thickening agent" constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Specification

8. The amendment filed September 16, 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "remove all of the thickening agent."

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Makino et al (US Pat. 6,399,305, June 4, 2002, filed June 7, 2000) in view of Blanchard (US Pat. 6,028,189, February 22, 2000; filed March 20, 1997) or Van Ness et al (US Pat. 6,248,521, June 19, 2001; filed July 21, 1998).

Makino et al. (herein referred to as Makino) teaches a method of producing DNA chips. Makino teaches DNA fragments having a reactive group on one end can be fixed onto an electroconductive substrate by spotting onto the substrate an aqueous solution containing the DNA fragment (col. 6, lines 40-45). The aqueous solution may contain a viscosity increasing additive such as sucrose, poleythlene glycol or glycerol (col. 6, lines

47-50). Polyethylene glycol is any of a family of colorless, water-soluble liquids with molecular weight from 200-6000. Sucrose is water-soluble and comprises a chain of simple sugars. The DNA fragment is fixed onto the substrate by covalent bonding (col. 6, lines 55-56). After the incubation is complete, the free DNA fragment is washed (col. 6, lines 56-58). Inherently, the thickening agent will be also washed away to some extent. In one specific example, Example 6-1, Makino teaches preparing a PNA chip on a gold electrode surface by forming a free vinylsulfonyl group on the electrode surface; spotting aqueous solution; allowing the solution to stand; and finally removing the free PNA fragments by washing with distilled pure water (col. 19-20)(limitations of Claim 5).

Makino teaches using a thickening agent to increase the viscosity. Makino teaches that the additive may be sucrose, a water-soluble polymer. A polymer is defined as any macromolecule which can be found within a living thing, such as proteins (essentially long chains of amino acids), nucleic acids (such as DNA or RNA), and polysaccharides (long chains of simple sugars). Makino does not particularly point out that the viscosity of the thickening agent is between 2-50 mPas.

However, Blanchard teaches a method of preparing micro-arrays which comprises (a) spotting onto a solid carrier an aqueous solution which contains a thickening agent and probe molecules having a reactive group to produce covalent bonding wherein the probe molecules may be a fragment of a nucleic acid, namely a single nucleotide monomer (b) spotting a second aqueous solution comprising a thickening agent and probe molecules; incubating the solid carrier having the aqueous solutions on the surface to produce the covalent bond and washing the surface of the

solid carrier with an aqueous medium to remove the thickening agent from the surface of the solid carrier. Specifically, Blanchard teaches a method of assembling arrays of oligonucleotides on a solid support which couples a first nucleotide monomer to a second nucleotide monomer in a high surface tension solvent, such as propylene carbonate (col. 2, lines 48-55). The method of step-by-step synthesis of an array of different chemical compounds at microdropsized loci, where each compound is covalently attached to the surface of a substrate comprises (a) spotting at least one microdrop of a first reagent in propylene carbonate to said surface which is chemically prepared to react with said first reagent to covalently attach said reagent to said substrate; (b) spotting onto the solid carrier in an area other than the area in which the aqueous solution was spotted, namely displacing the dispenser relative to the surface to apply a second microdrop; (c) allowing the substrate to form covalent bondings; (d) washing said carrier substrate to remove unattached reagents (col. 3, lines 25-50). The high surface tension solvent for the nucleotide monomers can be propylene carbonate which has a high boiling point, high viscosity, and high surface tension such that the solvent is amenable to a microfabricated ink-jet pump apparatus. Blanchard teaches that suitable solvents include propylene carbonate; acetonitrile; ethylene carbonate, HMPA and dimethyl sufoxide (col. 4, lines 65-68). Propylene carbonate has a viscosity of 2.5 centipoise (col. 4, lines 60-65). It is noted that the abbreviation cP denotes a unit of viscosity equal to a centipoise, also equal to one millipascal second (mPa s). Moreover, the synthesis method exist for the covalent bond formation between the 5' positions of two nucleotide monomers, or between the 5' position of a

nucleotide monomer and the 5' position of an oligonucleotide chain (col. 5, lines 35-40)(limitations of Claim 13). The number of cycles is indicative of the length of the oligonucleotides (col. 9, lines 12-16)(limitations of Claim 8, 16). As provided in Example II, two dimensional oligonucleotide arrays were synthesized. On a glass microscope slide, the slide was derivitized by treating with glycidoxypropyl silane and tetraethylene glycol (col. 11, lines 40-45). Using ink jets, a 0.1 molar solution of one of the four nucleotide phosphoramidites was dissolved in propylene carbonate, namely an aqueous solution with a thickening agent (col. 11, lines 50-58). A 42pL drop was delivered to the glass slide and the reaction was allowed to proceed for 30 to 60 seconds under an inert atmosphere, namely a coupling step. The slide was rinsed with acetonitrile then dipped in iodine, pyridine and water, ie. washing the surface of the carrier to remove some thickening agent (col. 11-12).

Additionally, Van Ness et al. (herein referred to as Van Ness) teaches a method of spotting nucleic acids on a silcon wafer or glass slide. Van Ness teaches printing (delivering or applying) oligonucleotides on a solid substrate in a regular pattern and allowing the polymers to dry. Van Ness teaches that solutions with viscosity enhancing chemicals such as glycerol provide especially improved handling capabilities using hydrophilic surfaces (col. 7, lines 15-17). Van Ness teaches that the 5' amine on the oligonucleotide may be reacted with a cross-linker such that the oligonucleotide is covalently attached to the polymer coating on the solid support. A "typical procedure" uses a solution of nucleic acid uniformly mixed in 57% glycerol and printed onto the solid support (col. 7, lines 30-35). The arraying solution is made with 56% glycerol and

44% water colored with blue food color (col. 19, lines 58-60). An arraying tip is used to spot solution into many microspots on a silicon wafer (col. 19, lines 59-63). The array is then washed in water (col. 20, lines 10-20). Inherently, the thickening agent and water-soluble polymer, namely glycerol, will be also washed away to some extent. It is noted that the abbreviation cP denotes a unit of viscosity equal to a centipoise, also equal to one millipascal second (mPa s). A fluid comprising 50% water and 50% glycerol, and having a viscosity of about 5 centipoises. A fluid comprising 38% water and 62% glycerol, and having a viscosity of about 10 centipoises. Therefore, based upon the examiner's calculation a solution of 56% glycerol and 44% water falls within the scope of claim 1.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the teachings of Makino for making arrays with vinylsulfonyl/amino attachments with the teachings of Van Ness and Blanchard desribing appropriate viscosities for thickening agents. While Makino does not specifically teach an appropriate viscosity for the aqueous solution which may contain a viscosity increasing additive such as sucrose, poleythlene glycol or glycerol (col. 6, lines 47-50), both VanNess and Blanchard teach particlular viscosities which were thickened. The ordinary artisan would have been motivated to have increased the viscosity of the aqueous solution within the ranges taught by VanNess and Blanchard. Blanchard teaches a viscosity of about 10 centipoises. Van Ness teaches a viscosity of about 2.5 centipose for propylene carbonate. Therefore, increasing the

viscosity to the art taught viscosity would have been obvious using sucrose given the teachings of Makino that sucrose may be added for increased viscosity.

With respect to removing all of the thickening agent, currently required by Claims 1 and 9, the skilled artisan would be motivated to remove the sucrose from the glass slide to ensure that polymer did not interact with further hybridization or analytical methods performed using the glass micro-array.

10. Claims 9, 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Makino et al (US Pat. 6,399,305, June 4, 2002, filed June 7, 2000) in view of Blanchard (US Pat. 6,028,189, February 22, 2000; filed March 20, 1997) or Van Ness et al (US Pat. 6,248,521, June 19, 2001; filed July 21, 1998) as applied to Claims 1, 5-8 above, and further in view of Vinayak et al (US Pat. 6,255,476, July 2001).

Neither Makino, Blanchard or Van Ness specifically teach immobilizing nucleic acid molecules through an amino group on the solid support and a phosphoric acid group on the nucleic acid probe molecules.

However, Vinayak et al. (herein referred to as Vinayak) teaches a method of synthesizing oligonucleotides on solid supports. Vinayak illustrates an oligonucleotide attached via an amino phosphoric acid group attachment. As see in in the depiction of the support, S is a solid support, Y may be an NH (amine group) and P1 may be an oligonucleotide (as seen in Figure 1). The 5' terminus of the oligonucleotide is attached to the solid support.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the covalent attachment means of the nucleic acid and support taught by Makino with the attachment means of the probe to the support taught by Vinayak. The ordinary skilled artisan would have recognized that any means of attachment of the probe to the solid support would have functioned to immobilize the nucleic acid probe to the solid support. Thus, the ordinary artisan would have been motivated to have attached the nucleic acid using any available means for immobilization including the phosphoric acid group and amino group method of Vinayak. Therefore, the ordinary artisan would have been motivated to have used a viscosity increasing additive, as in the method of Mankino, to apply the oligonucleotide comprising a 5' phosphorous linking group to the amino groups present on the solid support of Vinayak. Using the non-covalent bond with a cleavable linker, as taught by Vinayak would allow the ordinary artisan to remove the immobilized oligonucleotides easily. The ordinary artisan would have recognized the ability to attach the oligonucleotide of Vinayak to the solid support using the method of Mankino to add viscosity to the aqueous solution.

Conclusion

11. No claims allowable over the art.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
November 12, 2003

BJ FORMAN, PH.D.
PRIMARY EXAMINER